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| EXAMINER | |
|---|---|
| HOWARD, ZACHARY C | |
| **ART UNIT** | **PAPER NUMBER** |
| 1646 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/772,090 | BARON ET AL. | |
| | Examiner | Art Unit | |
| | Zachary C. Howard | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *1-42 and 44-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-56* are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/3/2004; 1/9/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicants' election with traverse of Group VI, claim 43, in the reply filed on 1/8/07 is acknowledged.

The traversal is on the ground(s) that "a search of at least Groups V and VI simultaneously would not substantially increase the burden on the examiner."

This is not found persuasive because the inventions of Groups V and VI are distinct as set forth in the restriction requirement mailed 10/4/06. Group V is claims 31, 35 and 37, as drawn to treatment of a subject for excess erythroid cells. Group VI is claim 43, drawn to treatment of a subject for abnormally enhanced vascular growth. These methods of treatment are related in that a similar genus of compounds (inhibitory hedgehog compounds) is used in each method. However, related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants. Further, the inventions as claimed are not capable of use together, and also have a materially different mode of operation and function. In particular, the methods are for treatment of disorders associated with different cell differentiation processes (hematopoiesis versus vascular growth). Therefore, the affected tissues and patient populations to be treated are different and non-overlapping in each method. Because these inventions are distinct and/or unrelated for the reasons given above and have acquired a separate status in the art as shown by their different classification, separate search requirements and/or divergent subject matter, restriction for examination purposes as indicated is proper.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-42 and 44-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable

generic or linking claim. Applicants timely traversed the restriction (election) requirement in the reply filed on 1/8/07.

Claim 43 is under consideration.

***Specification***

The disclosure is objected to because of the following informalities:

(1) The title ("Methods of modulating hematopoiesis and vascular growth") of the invention is not descriptive. Specifically, the claim is limited to treatment of enhanced vascular growth in a subject using an inhibitory hedgehog compound, whereas the current title broadly encompasses a variety of non-claimed methods such as modulation of hematopoiesis and upregulation of vascular growth. A new title is required that is clearly indicative of the invention to which the claim is directed.

(2) An updated priority statement of the instant application's parent provisional and nonprovisional applications should be included in the first sentence of the specification or application data sheet. It is noted that Applicants have filed an Application Data Sheet (ADS) on 2/3/04. However, said ADS is missing the Application number of the instant application on pages 1 and 2 of the ADS. Furthermore, the priority information does not indicate that application 09/021660 issued as U.S. Patent No. 6713065 on 3/30/04. It is noted that the first sentence of the specification was amended by preliminary amendment on 2/3/04 to indicate that the instant application is a continuation of U.S. 09/021660, but does not indicate that application 09/021660 issued as U.S. Patent No. 6713065 on 3/30/04. Applicants should amend either the ADS or first sentence of the specification to reflect the correct current priority information.

(3) The disclosure is objected to because the Brief Description of the Figures is missing a reference to each part of each Figure. See 37 CFR § 1.74, which states "When there are drawings, there shall be a brief description of the several views of the drawings and the detailed description of the invention shall refer to the different views by specifying the numbers of the figures and to the different parts by use of reference letters or numerals (preferably the latter)" and MPEP 601.01(g) which states "if the

drawings show Figures 1A, 1B, and 1C and the brief description of the drawings refers only to Figure 1, this is an error in the specification which must be corrected."

Specifically, the specification is missing a reference to the following parts of the Drawings filed on 2/3/2004:

(a) Figure 2 includes parts 2A, 2B, 2C, 2D, 2E and 2F. However, the Brief Description of Figure 2 on page 6 of the specification does not refer to each of these parts.

(b) Figure 7 includes parts 7-1A, 7-1B, 7-1C and 7-1D (on sheet 6) and parts 7-2A, 7-2B, 7-2C, 7-2D and 7-2E (on sheet 7). However, the Brief Description of Figure 7 on pages 7 and 8 of the specification does not refer to each of these parts.

(c) Figure 8 includes part 8-1A, 8-1B and 8-1C (on sheet 8) and part 8-2 (on sheet 9). However, the Brief Description of Figure 2 on page 8 of the specification does not refer to each of these parts.

(d) Figure 14 includes parts 14-A, 14-B, 14-C and 14-D (on sheet 14) and parts 14-E and 14-F (on sheet 15). However, the Brief Description of Figure 14 on page 9 of the specification does not refer to each of these parts.

Appropriate correction is required.

### *Claim Rejections - 35 USC § 112, 1st paragraph, enablement*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 43 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue"

include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is a method of treating abnormally enhanced vascular growth in a subject with a hedgehog compound capable of inhibiting the activity of a gene product expressed in an extraembryonic tissue. The term "vascular" refers to vessels that circulate biological fluids such as blood or lymph; therefore "vascular growth" includes vasculogenesis and angiogenesis of blood and lymph vessels. With respect to blood vessels the relevant art teaches, "[i]n vasculogenesis, endothelial cells are differentiated *de novo* from mesodermal precursors, whereas in angiogenesis, new blood vessels are generated from pre-existing ones. Vasculogenesis occurs only during embryonic development and leads to formation of a primary capillary plexus. In angiogenesis, new capillaries form and remodel by budding (sprouting), splitting (intussusception) and fusion (intercalated growth), producing a juvenile vascular system and then a mature one" (pg 2013 of Cohen Jr, 2006. American Journal of Medical Genetics. 140A: 2013-2038). However, other teachings in the relevant art suggest that vasculogenesis may also contribute to blood vessel formation in adult mammals; however, the role of this contribution is not well-characterized (see pg 157 of Ribatti et al. 2001. Mechanisms of Development. 100: 157-163).

The claim is extremely broad with respect to the encompassed conditions related to vascular growth. Treatment of "enhanced vascular growth" includes abnormally enhanced vascular growth that occurs in either embryonic vascularization or adult angiogenesis. The specification teaches that conditions of "excess vascularization" or "neovascularization" include "a variety of solid tumors such as breast cancer, hemangiomas in infancy, ocular neovascularization associated with diabetes, bleeding disorders of the female reproductive tract, and certain forms of arthritis" (pg 28, lines 10-13). The specification further teaches, "abnormal vascular growth such as occurs in tumors, rheumatoid arthritis, hemiangiomas, angiofibromas, psoriasis and capillary

proliferation and diabetes" (pg 2 lines 22-24). The specification further teaches, "a method is further provided for treating abnormal blood vessel formation (hypervascularization) resulting from genetic diseases, chronic degenerative disease, aging, trauma, or infectious agents. Examples include diabetic chronic ulcers, bums, frost bite, ischemic events following stroke and transplantation" (pg 27, lines 26-30).

The claim is also extremely broad with respect to the "hedgehog compound" to be used for treatment. The specification teaches that a ""[h]edgehog compound" is defined here and in the claims as a class of molecules of the hedgehog family that includes recombinant hedgehog protein, analogs, and derivatives of hedgehog proteins, and agonists and antagonists of hedgehog protein receptors and functional equivalents of the aforementioned" (pg 11, lines 23-26). This definition places no limitation on the structure of an "analog" or "derivative" of a hedgehog compound, or on the structure of an "agonist" or "antagonist" of hedgehog protein receptors. Therefore, the genus of "hedgehog compound" is vast because no structural limitation is placed on genus members. The specification further provides the following examples of "hedgehog compounds": hedgehog compounds described in WO 95/18856 and here incorporated by reference, including homologs of hedgehog proteins, recombinant hedgehog proteins, hedgehog encoding nucleic acids, antisense molecules, gene constructs for use in gene therapy including viral vectors known in the art, combinatorial mutants of hedgehog proteins as agonists or antagonists, and antibodies specific for hedgehog protein epitope" (pg 22, lines 19-23).The scope of the encompassed "hedgehog compound" is also broad with respect to the functional language; i.e., the phrase "capable of inhibiting the activity of a gene product expressed in extraembryonic tissue" encompasses any gene expressed in extraembryonic tissue". The relevant art teaches expression of a "large number of genes in extraembryonic tissues" including at least 8,500 genes that exhibit differential regulation in placentae during pregnancy (see pgs 70-71 of Ishida et al. 2007. Journal of Reproduction and Development. 53(1): 69-76).

In contrast to the extreme breadth of the claim, the specification as originally filed provides minimal guidance to the skilled artisan with respect to practicing the claimed method. The specification does not provide any *in vivo* working examples of treatment

of a condition of "abnormally enhanced vascular growth" with a "hedgehog compound". The specification does not provide any *in vitro* models that correlate with *in vivo* treatment. The specification does not guidance regarding the levels of hedgehog expression in any subjects with "abnormally enhanced vascular growth", or how to administer particular "hedgehog compounds" such that enhanced vascular growth will be inhibited.

Examples 3-6 of the specification provide teachings that are very limited in relation to the claimed inventions. Example 3 teaches that exogenous Sonic hedgehog (Shh) protein added to explant culture can "stimulate hematopoiesis in the epiblast mesoderm" in place of visceral mesoderm (pg 44, lines 6-20). Hematopoiesis was assessed by measuring ε-globlin (see description of Figure 9 on pg 8), which the specification teaches as a marker of erythroid cell formation (pg 28, lines 20-21). Example 3 further teaches that Shh or Indian Hedgehog (Ihh) proteins stimulate proliferation adult hematopoietic stem cells isolated from bone marrow and cultured. Example 4 demonstrates that "Shh blocking antibody" reduces ε-globlin expression in cultured murine whole embryo (pg 48). Example 5 demonstrates expression of *patched* and *Gli* (genes that encode hedgehog signaling pathway components) that was "substantially exclusive in the yolk sac mesoderm" (pg 48). Example 6 states that, "both *Indian hedgehog* and *BMP-6* are expressed in early visceral endoderm." Based on these results, the specification asserts that hedgehog proteins "have utility in regulating hematopoiesis and vascular growth in the adult animal" (pg 13, lines 24-25). However, these examples in the specification are all related to *in vitro* hematopoiesis rather than vascular growth, and hematopoiesis is a different molecular process from vascular growth. As taught in the specification, "[i]n contrast to vascular growth, hematopoiesis is normally a continuous process throughout the life of an adult" (pg 2, lines 26-27). There are no examples related to stimulation or inhibition of vascular growth in either an embryo or an adult. Furthermore, abnormal vascular growth in adult subjects does not necessarily involve expression of the same molecules in different conditions. For example, vascular endothelial growth factor (VEGF), a molecule associated with angiogenesis, demonstrates expression that is variable, "not only among different

tumour types, but also with the same tumour" (pg 394 of Ferrara et al. 2004. Nature Reviews Drug Discover. 5(3): 391-400). Therefore, the skilled artisan could not predict whether or not any particular condition of enhanced vascular growth could be inhibited by a "hedgehog compound capable of inhibiting the activity of a gene product". In view of the lack of guidance provided by the specification and the prior art the skilled artisan could not practice the claimed method without undue experimentation. The examples in the specification do not provide sufficient guidance to predict whether or not inhibition of "a gene product expressed in an extraembryonic tissue" will result in treatment of enhanced vascular growth.

Furthermore, the claim encompasses treatment of diseases associated with enhanced vascular growth wherein inhibition of angiogenesis is contrary to treatment of the disease. The abnormally enhanced angiogenesis that occurs in ischemia is advantageous for survival of the affected subject rather than harmful and it is not predictable how a 'hedgehog compound' that is an angiogenic inhibitor could be used for treatment of ischemia. In addition, treatment of ocular neovascularization associated with diabetes with anti-angiogenic compound is problematic; for example Cohen Jr (2007) teaches, "extensive research is necessary to understand how to treat retinal neovascularization in diabetics because antagonism of VEGF might interfere with myocardial revascularization" (pg 2033 of Cohen Jr, 2007; cited above).

Furthermore, the specification does not provide sufficient guidance to select a "hedgehog compound capable of inhibiting the activity of a gene product expressed in an extraembryonic tissue" without undue experimentation even if the gene product to be inhibited is Sonic hedgehog. The only specific inhibitor of Sonic hedgehog that is described in the specification is "Shh blocking antibody" (pg 48, line 19). However, as described above, the claim encompasses a vast number of potential inhibitory compounds and no guidance is provided as to structure of the compounds. For example, with respect to variants of the hedgehog protein that are antagonists, Applicants have not given any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property, or defined a difference in structure, or difference in function, between a wild type hedgehog protein and variants

of said protein. The specification refers to WO 95/18856 (also cited on the 2/3/04 IDS) as teaching hedgehog compounds; however, the '856 publication only describes naturally occurring vertebrate hedgehog proteins and does not describe any variants that are antagonists. The '856 publication merely invites the skilled artisan to engage in screening a large number of variant sequences to search for an antagonist protein. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, it may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues;

therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39; Doerks *et al.* (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427].

Furthermore, significant unpredictability with regard to the mode of administration of the compound used in the claimed method. The specification provides no guidance as how to administer specific "hedgehog compounds" for treatment. As taught in the relevant art, many years after filing of the instant application, "[t]he pharmacokinetics of various angiogenic inhibitors are very complex, and the method of administration can have a significant effect on efficacy" (pg 2017 of Cohen J, 2006; cited above). Furthermore, the claim encompasses methods of treatment by administration of proteins (protein therapy) and/or administration of nucleic acids (gene therapy), which at the time of filing of instant application had significant elements of unpredictability.

Overall, the relevant literature reports that the goal of delivering proteins and peptides non-invasively has only achieved modest success, with poor applicability to proteins and peptides (see pg 343, col 1-2 of Pettit et al. 1998. Trends Biotechnol. 16: 343-349.) The problems posed by proteins and peptides are their large molecular size, electrical charge, relatively hydrophilic nature, and relative instability in environments of extreme pH or proteolytic activity (such as the stomach and intestine) (pg 343, col 2). Pettit reviews several routes of protein administration and the limitations that have been encountered. For example, limited success has been achieved delivering proteins and peptides orally because of: 1) poor intrinsic permeability across intestinal epithelium, 2) susceptibility to enzymatic attack, 3) rapid post-absorptive clearance, and 4) chemical

instability (pg 344-345). Direct injection of protein or peptide drugs into the brain is undesirable because diffusion of these molecules is poor in parachymal brain tissue (pg 346, col 2). The delivery of proteins and peptides to the surface of the eye is complicated by normal process of blinking, tearing, and drainage form the eye (pg 346, col 2). Although much effort has been given to the transdermal delivery of pharmaceutical products, clinical applications have been limited to non-protein drugs because of the skin's poor permeability to proteins and peptides (pg 343, col 2). Additionally, proteins or peptides administered systemically must resist clearance via molecular filtration by the kidney and clearance by the reticuloendothelial system (pg 345, col 2). Therefore, the state of the prior art establishes the unpredictability of delivering proteins to a subject.

The specification also discloses that nucleotide constructs can be used in gene therapy approaches (pg 22, lines 21-22). However, the specification does not teach any methods or working examples that indicate a nucleic acid is introduced and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vector would introduce the claimed nucleic acid into the cell or in what quantity and duration. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001; abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express the claimed nucleic acid into the cell of an organism to treat disease.

Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express the claimed nucleic acid in the cell of an organism or be able to produce the encoded protein in that cell.

In summary, it is acknowledged that the level of skill of those in the art is high, but it is not disclosed and not predictable from the limited teachings of the prior art and specification how to make and use a hedgehog compound to treat abnormally enhanced vascular growth. There are no examples of treatment of abnormally enhanced vascular growth with a "hedgehog compound". Thus the specification fails to teach the skilled artisan how to use the hedgehog compounds as a therapeutic reagent without resorting to undue experimentation. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use the claimed method for the above stated purpose. Due to the large quantity of experimentation necessary to determine how to make and use a hedgehog compound for treatment of abnormally enhanced vascular growth, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention. What Applicants have provided is a mere wish or plan and an invitation to experiment.

***Claim Rejections - 35 USC § 112, 1st paragraph, written description***

Claim 43 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicants are claiming and what Applicants have possession of.

Claim 43 is a genus claim because the claim is directed to method of using a vast genus of compounds. These compounds must be: (1) a "hedgehog compound

capable of inhibiting the activity of a gene product expressed in a extraembryonic tissue" and (2) effective in "inhibiting abnormally enhanced vascular growth" when administered to a subject with abnormally enhanced vascular growth.

The specification teaches that a ""[h]edgehog compound" is defined here and in the claim as a class of molecules of the hedgehog family that includes recombinant hedgehog protein, analogs, and derivatives of hedgehog proteins, and agonists and antagonists of hedgehog protein receptors and functional equivalents of the aforementioned" (pg 11, lines 23-26). This definition places no limitation on the structure of an "analog" or "derivative" of a hedgehog compound, or on the structure of an "agonist" or "antagonist" of hedgehog protein receptors. Therefore, the genus of "hedgehog compound" is vast because no structural limitation is placed on genus members. The specification further provides the following examples of "hedgehog compounds": hedgehog compounds described in WO 95/18856 and here incorporated by reference, including homologs of hedgehog proteins, recombinant hedgehog proteins, hedgehog encoding nucleic acids, antisense molecules, gene constructs for use in gene therapy including viral vectors known in the art, combinatorial mutants of hedgehog proteins as agonists or antagonists, and antibodies specific for hedgehog protein epitope" (pg 22, lines 19-23).

No hedgehog protein is described in the specification as being an inhibitor. The specification refers to WO 95/18856 as describing hedgehog compounds; however, the '856 publication only describes naturally occurring vertebrate hedgehog proteins and does not describe any specific variants that are antagonists. With regard to antagonists of hedgehog protein receptors, the specification describes a single functional example: a "SHH blocking antibody" (pg 48, line 19).

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in

possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of "hedgehog compounds" to be used in the claimed methods. There is not even identification of any particular portion of the structure that must be conserved. Structural features that could distinguish encoded inhibitory compounds in the genus from other potential compounds are missing from the disclosure. The specification and claim do not provide any description of what changes should be made. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and polypeptides encompassed. Thus, no identifying characteristics or properties of the instant inhibitory "hedgehog compounds" are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed" (pg 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (pg 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written

description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a method of using a hedgehog compound that is a SHH blocking antibody, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicants are reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see pg 1115).

***Conclusion***

The claim is not allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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